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Chapter 76. Fibrous Dysplasia

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INTRODUCTION

Fibrous dysplasia of bone (FD; OMIM#174800) is an uncommon skeletal disorder with a broad spectrum of clinical expressions, ranging from an incidentally discovered asymptomatic radiographic finding, involving a single skeletal site, to a severe disabling disease. The disease may involve one bone (monostotic forms), multiple bones (polyostotic FD), or even the entire skeleton (panostotic FD). In polyostotic forms, lesions of different limb bones are often (but not necessarily) ipsilateral.[1] FD may associate with extraskeletal lesions or dysfunction, most commonly cutaneous pigmentation (Figs. 1A and 1B) and hyperfunctioning endocrinopathies including precocious puberty, hyperthyroidism, growth hormone (GH) excess, and Cushing syndrome (McCune-Albright syndrome [MAS]).[2] A renal tubulopathy, which includes renal phosphate wasting, is one of the most common extraskeletal dysfunctions associated with polyostotic disease.[3] More rarely, FD may be associated with myxomas of skeletal muscle (Mazabraud's syndrome)[4] or dysfunction of heart, liver, pancreas, or other organs in the context of the MAS.[5]

ETIOLOGY AND PATHOGENESIS

All forms of FD are caused by activating, missense mutations of the *GNAS1* gene, encoding the α subunit of the

The authors have no conflict of interest.

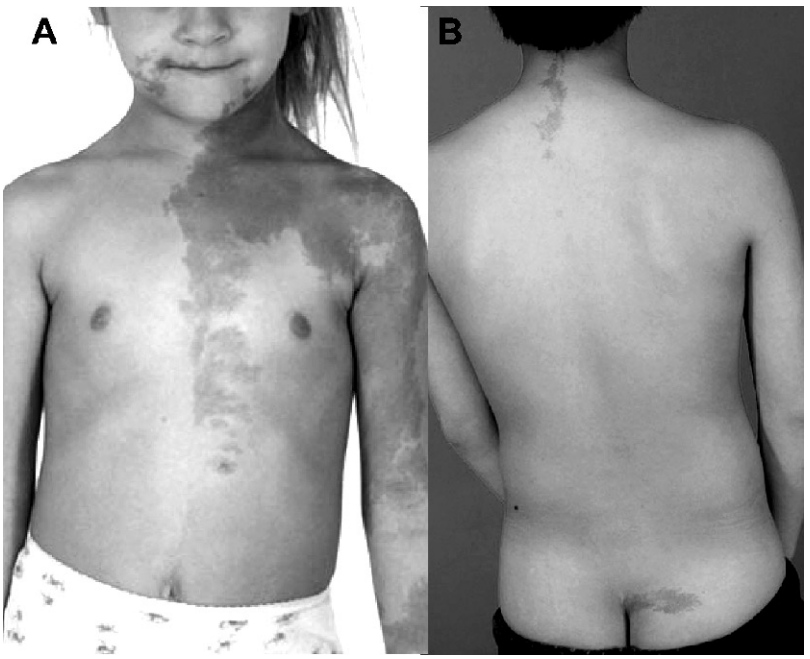

FIG. 1. Café-au-lait skin pigmentation. (A) A typical lesion on the face, chest, and arm of a 5-year-old girl with McCune-Albright syndrome, which shows jagged "coast of Maine" borders and the tendency for the lesions to both respect the midline and follow the developmental lines of Blashko. (B) Typical lesions that are often found on the nape of the neck and crease of the buttocks are shown.

stimulatory G-protein, $G_s\alpha$.[6,7] Mutations occur postzygotically, are never inherited, and result in a somatic mosaic state. Time of mutation occurrence in development, and size and viability of the mutated clone arising from the single originally mutated cell determine the variable distribution and frequency of the mutated cells in the postnatal organism and the extent and severity of disease.[1] Single base transitions lead to replacement of arginine at position 201 with histidine or cysteine (most commonly) or rarely with other amino acids.[8] As a consequence of the mutation, the catalysis of guanine triphosphate (GTP) to guanine diphosphate (GDP) by $G_s\alpha$ is significantly lowered. Constitutive activation of adenylyl cyclase by the mutated $G_s\alpha$ ensues, and the resulting excess cyclic adenosine monophosphate (cAMP) mediates a number of pathological effects in mutated cells.[1] In bone, mutations impact on cells of the osteogenic lineage, with adverse effects both on osteoprogenitor cells and differentiated osteoblasts.[9,10] Expansion of the osteoprogenitor cell pool leads to their accumulation in marrow spaces, resulting in local loss of hematopoietic tissue and marrow fibrosis. Osteogenic cells derived from mutated skeletal progenitors are functionally and morphologically abnormal and deposit abnormal bone. Bone trabeculae are abnormal in shape (so-called Chinese writing, alphabet soup patterns), collagen orientation, and biochemical composition,[9] and in many cases, are severely undermineralized and abnormally compliant[9,11] (Fig. 2E). The histological pattern may be significantly different at different skeletal sites, and peculiar patterns are seen in craniofacial bones.[12] The hormonal climate influences FD lesions[13] and may significantly alter the local rate of bone remodeling.[11] FD tissue is highly vascularized and therefore prone to bleeding, leading to posthemorrhagic cysts.[14] Arteriovenous shunts are formed, which may, in rare cases, lead to high-output cardiac failure in the presence of extensive skeletal involvement.

CLINICAL FEATURES

Pathological effects of $G_s\alpha$ mutations in osteogenic cells are most pronounced and evident during the phase of rapid bone growth, which translates into the most common clinical presentation during childhood or adolescence.[15] Presentation in infancy is rare and usually heralds severe, widespread disease with multiorgan involvement. Pain, fracture, and deformity are the most common presenting features. In general, children are less likely to complain of pain, per se, and may instead report stiffness or tiredness. In adults, the complaint of pain is common, especially in the ribs, long bones, and craniofacial bones. It is often severe and may require narcotic analgesics. Lesions in the spine and pelvis are usually less painful. Pathological fracture, or stress fracture of weight bearing limb bones, is a prime cause of morbidity. Deformity of limb bones is caused by expansion and abnormal compliance of lesional FD, fracture treatment failure, and local complications such as cyst formation.[1] Deformity of craniofacial bone is solely the result of the overgrowth of lesional bone.

Although any bone may be affected, the skull base and the proximal metaphysis of the femora are the two sites most commonly involved. Femoral disease usually presents in childhood with, limp, fracture, pain, and deformity, ranging from coxa vara to the classical shepherd's crook deformity (Fig. 2A). Radiographically, the lesion may be limited to the metaphysis or extend along the diaphysis for variable length.[14] The picture most commonly observed in children and adolescents consists of an expansile, deforming, medullary lesion, with cortical thinning and an overall "ground glass" density (Fig. 2A). The radiographic picture is significantly affected by the evolution of the lesion over time and by the appearance of superimposed changes, most commonly aneurysmal bone cysts. Hence, lesions observed in

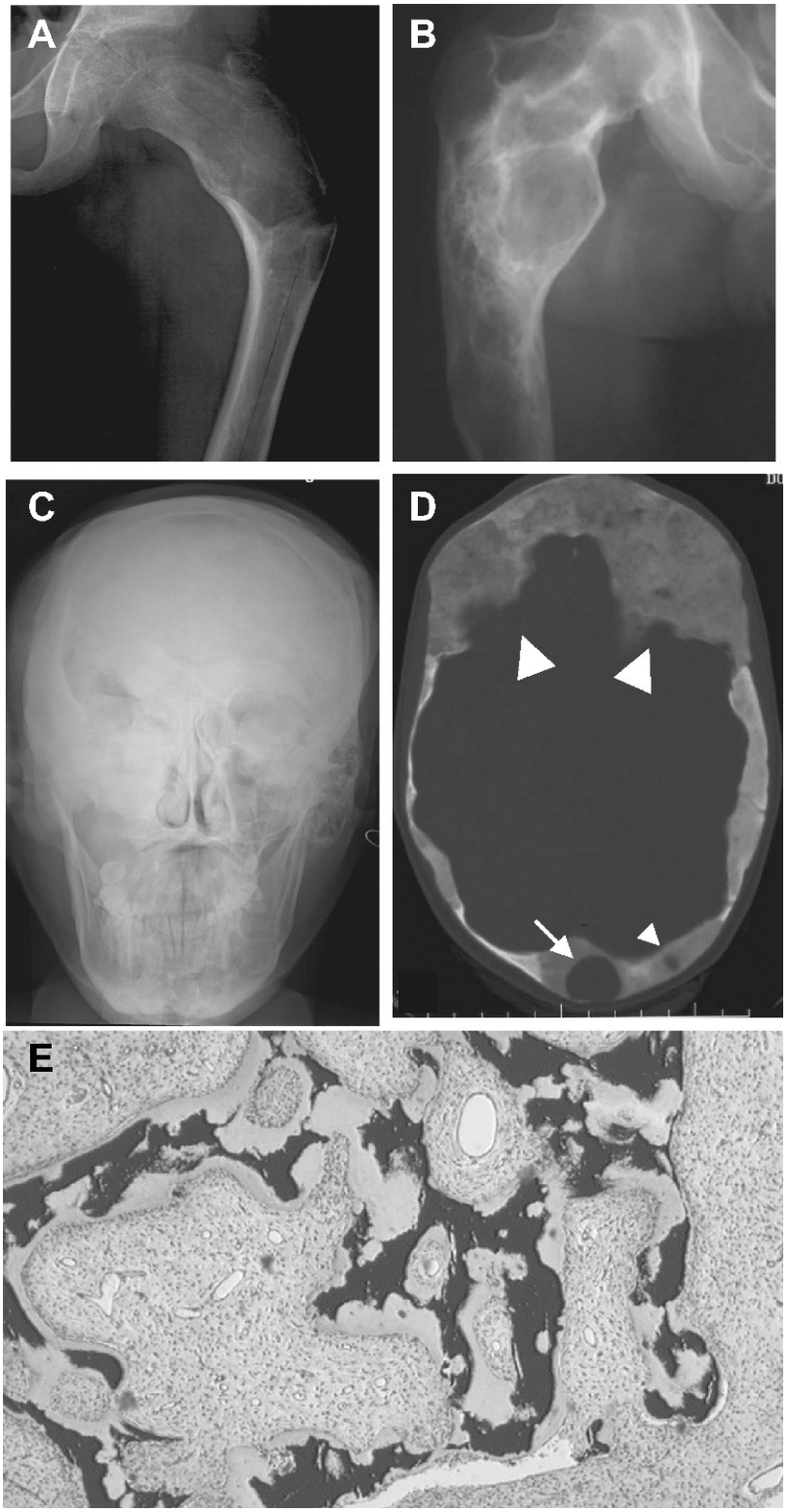

FIG. 2. Radiographic and histological appearance of FD. (A) A proximal femur with typical ground glass appearance and shepherd's crook deformity in a 10-year-old child is shown. (B) The appearance of FD in the femur of an untreated 40-year-old man show the tendency for FD to appear more sclerotic with time. (C) The typical sclerotic appearance of FD in the craniofacial region is shown. (D) A CT image show thickened frontal bone with a mixed solid and cystic appearance (large arrowheads), and lesions in the occipital bone, one with "cystic" changes (small arrowhead) that represents an area of fibrous tissue, as well as a fluid-filled cyst (arrow). (E) Representative histological image of FD. The tissue was processed for undecalcified embedding, which enables to show excess osteoid in the undermineralized fibrous dysplastic bone. The marrow spaces are filled with "fibrous" tissue, consisting of excess, abnormal marrow stromal cells.

adults tend to appear more sclerotic and less homogeneous (Fig. 2B). Sclerosis in FD lesions of the femur and other limb bones, but not in craniofacial lesions, may signify less active disease.

In the skull, FD mostly involves the skull base and facial bones. The typical presentation is in childhood with facial asymmetry or a "bump" that persists, but symmetric expansion of malar prominences and/or frontal bosses may also be seen. The disease can progress into adulthood and disfiguration may be marked. Abnormal growth and deformity of craniofacial bones may result in encroachment on cranial nerves. Severe adverse consequences are rare,[16] but obvi-

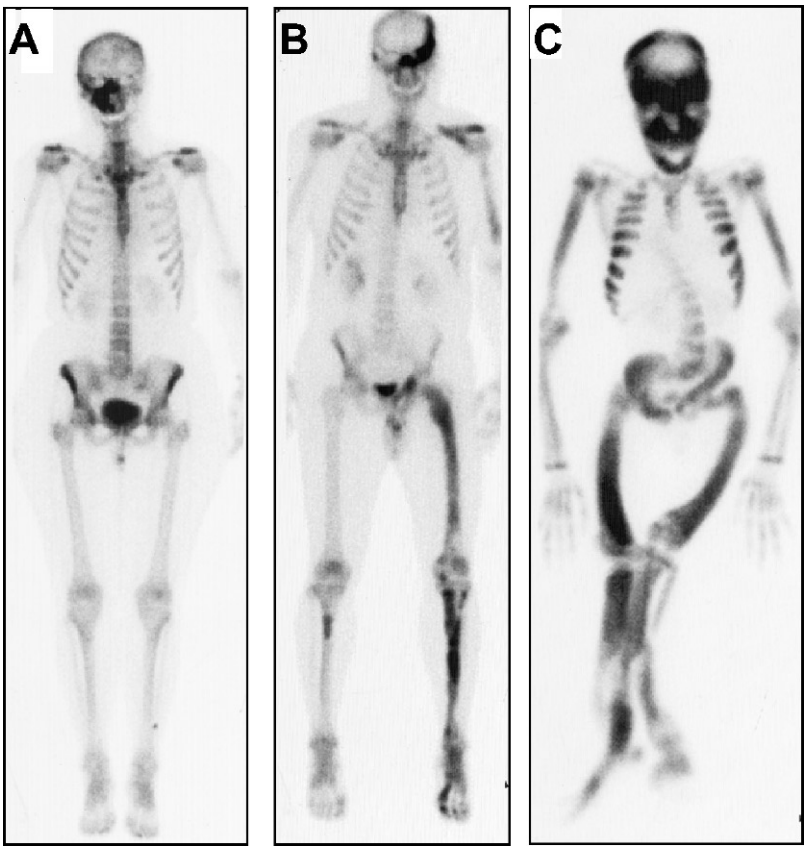

FIG. 3. Bone scintigraphy in FD. Representative ^{99}Tc-MDP bone scans that show tracer uptake at affected skeletal sites are shown. (A) A 50-year-old woman with monostotic FD confined to a single focus involving contiguous bones in the craniofacial region. (B) A 42-year-old man with polyostotic FD shows the tendency for FD to be predominantly (but not exclusively) unilateral and to involve the skull base and proximal femur. (C) A 16-year-old boy with McCune-Albright syndrome and involvement of virtually all skeletal sites (panostotic) is shown.

ously represent one of the most important concerns. FD tissue in craniofacial bones is especially prone to bleeding, herniation through cranial foramina and vascular passages, and formation of posthemorrhagic cysts (Fig. 2D). These events may precipitate blindness when they occur in the vicinities of the optic nerves. Craniofacial FD may have a "ground glass" appearance, but a sclerotic, "pagetoid" appearance is typical (Fig. 2C), and correlates with site-specific, osteosclerotic, histological changes.[12] Lesions in the spine, ribs, and pelvis are common, may be elusive on plain radiographs, and are easily detected by bone scintigraphy, the most sensitive imaging technique for the detection of FD lesions (Fig. 3). Disease in the spine is frequently associated with scoliosis, which may be progressive and require surgery.

Malignancy in FD is rare ($<1\%$).[17] While there is an association with the development of cancer with prior treatment with high dose external beam radiation, it may occur independent of prior exposure to ionizing radiation. Rapid lesion expansion and cortical bone disruption should alert the clinician to the possibility of sarcomatous change. Osteogenic sarcoma is the most common, but not the only type of bone tumor that may complicate FD. The clinical course is usually aggressive, surgery is the primary treatment, and chemotherapeutic regimens do not seem to improve prognosis significantly.

MANAGEMENT AND TREATMENT

Diagnosis of FD must be established based on expert assessment of clinical, radiographic, and histopathological features. Markers of bone turnover are usually elevated.[3] Disease extent is best determined with total body bone scintigraphy, and potential associated metabolic derangements must be accurately screened for and specifically treated. These include not only endocrine dysfunction, but also the occurrence of renal phosphate wasting and hypophosphatemia. Some endocrine dysfunction (e.g., GH excess, Cushing's disease) may significantly affect the course of the skeletal disease.[13] Phosphate wasting impairs the mineralization of FD bone, aggravating deformity and tendency to fracture.[11]

Mutation analysis may be helpful in distinguishing FD from unrelated fibro-osseous lesions of the skeleton, which may mimic FD both clinically and radiographically (osteofibrous dysplasia, ossifying fibromas of jawbones).[1] Multiple nonossifying fibromas, skeletal angiomatosis, and Ollier's disease may sometimes enter the differential diagnosis, which again relies on histology and mutation analysis.

Disease of the proximal femur, in which there is fracture or impending fracture, is often best treated by insertion of intramedullary nails, in an effort to prevent serious deformity and limb length discrepancy.[14,18] Design of specific types of nails is felt to be necessary, and development of such devices is underway.[14] Surgery is not advocated for craniofacial disease unless hearing or vision loss are documented and prophylactic optic nerve decompression appears to be contraindicated.[16] Treatment with bisphosphonates (pamidronate) has been advocated based on observational studies,[19,20] with claims of reduced pain, decreased serum

and urine markers of bone metabolism, and improvement in the radiographic appearance of the disease, but the effects of bisphosphonates on the natural history of FD remain to be determined in controlled studies.

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Chapter 77. Osteogenesis Imperfecta

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INTRODUCTION

Osteogenesis imperfecta (OI), sometimes called brittle bone disease, is a heritable disorder of connective tissue involving type I collagen.[1–3] The pathogenesis of all major types (Table 1) centers on a quantitative and often also a qualitative abnormality of this most abundant protein in bone.[1–3] The clinical hallmark of OI is osteopenia causing recurrent fractures and skeletal deformity.[4] However, type I collagen is also present in teeth, sclerae, ligaments, skin, and elsewhere, and many patients with OI have dental disease because of defective formation of dentin (*dentinogenesis imperfecta*).[5] Abnormalities can occur in other tissues that contain this fibrous protein.[1–3] Severity of OI is, however, extremely variable and ranges from stillbirth to perhaps lifelong absence of symptoms. The classification system devised by Sillence,[6] according to clinical features and apparent mode of inheritance, provided a useful framework for prognostication and further biochemical/molecular studies. However, this nosology has limitations, and DNA-based findings have elucidated, especially for the severe forms, the autosomal dominant inheritance pattern.[1–3] The clinical heterogeneity of OI is now understood because a great variety of dominant/negative mutations have been characterized within the two genes that encode the two different, large, protein chains (pro α_1 and pro α_2) that combine to form the type I collagen heterotrimer.[1–3,7]

CLINICAL PRESENTATION

Among the differential diagnosis for OI in infants and children is idiopathic juvenile osteoporosis, Cushing's dis-

The author has no conflict of interest.